REMARKS

The present application relates to a method of treating or inhibiting the growth of cancer cells by administering certain substituted triazolopyrimidines.

Claims 2-4, 6-8, 10-12, 14-15, 17-20, 22, 67, 74-77, 79-81, 83-85, 87-88, 90-93 and 95-98 are pending in the application. Applicants thank the Examiner for acknowledging the addition of "cervical cancer" to claim 67 by the applicants' amendment of May 16, 2005. Said amendment to claim 67 is supported by the specification and introduces no new matter. By the current amendment claims 2-3, 6-8, 11-12, 14, 17-18, 22, 75-76, 79-81, 84-85, 87, 90-91, 67, and 95 have been amended, claims 16 and 89 have been canceled .

In the office communication of August 9, 2005 the Examiner has retained the rejection of claims 2-4, 6-8, 10-12, 14-20, 22, 67, 74-77, 79-81, 83-85, and 87-93 and 95-97 under 35 USC §112, first paragraph, because the specification, while being enabling for the treatment of lung cancer, gliobastoma, melanoma, colon cancer and cervical cancer does not reasonably provide enablement for the treatment of other types of cancer, or the treatment of cancerous cells that express multiple drug resistance (MDR). Further, the Examiner has rejected claim 98 as being dependent on claim 67.

In response, applicants respectfully traverse the rejection and believe that the application is patentable under 35 USC §112, first paragraph and urge withdrawl of this rejection. While not nececessarily in agreement with the Examiner, applicants in order to advance prosecution have amended claims 2-3, 6-8, 11-12, 14, 17-18, 22, 75-76, 79-81, 84-85, 87, 90-91, 67, and 95 to overcome the Examiner's rejection 35 USC § 112 first paragraph. In response, applicants submit that claims 2-3, 6-8, 11-12, 14, 17-18, 22, 75-76, 79-81, 84-85, 87, 90-91, 67, and 95 as amended further comply with 35 USC § 112 first paragraph. Applicants submit that the dependent claims 4, 10, 15, 19-20, 74, 77, 83, 88, 92-93, and 96-97 also comply with 35 USC § 112 first paragraph. Applicants maintain that one of ordinary skill in the art would, in view of the applicants' written description in the specification, be able to use the

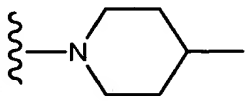
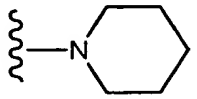
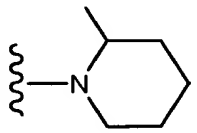
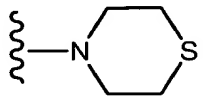
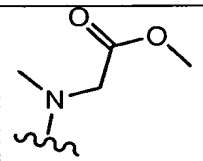
invention commensurate in scope with the claims as amended. Support for the claims as amended is found throughout the specification.

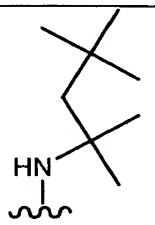
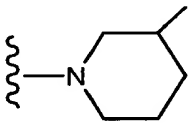
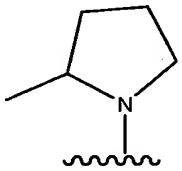
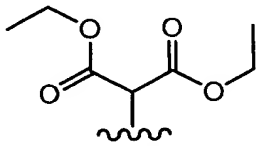
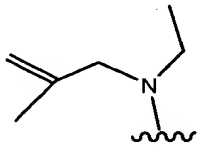
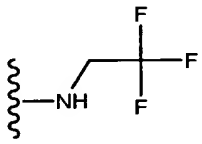
Applicants believe they have met the requirements of 35 USC §112, first paragraph and urge withdrawal of this rejection The applicants do not believe that the Examiner has set forth a proper basis for rejection of claim 98. It is rejected merely as being dependent on claim 67. If it was the Examiner's intention to object to the claim as being allowable except for being dependent upon a rejected base claim, applicants would have amended the claim to be independent and would do so if notified by the Examiner that it would place the claim in condition for allowance.

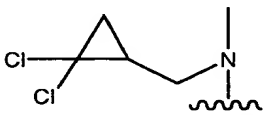
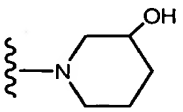
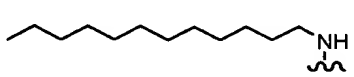
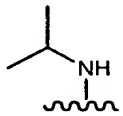
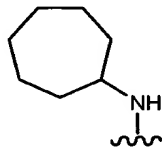
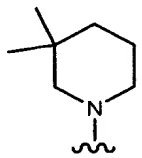
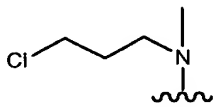
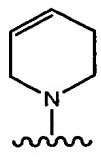
The Examiner also acknowledges that a large number of the compounds of Formula (I) were tested by applicants, but contends that the tested compounds of Formula (I) tend to have R^3 as Cl, R^4 as hydrogen, R^2 as phenyl substituted with fluoride (e.g., difluorophenyl, trifluorophenyl or trifluoromethyl-phenyl) and R^1 is not as extensively substituted.

In response, applicants respectfully traverse the rejections regarding substitutions at R^1, R^2, R^3 and R^4 as described by the Examiner. Applicants have provided in the specification, over 200 working examples and their corresponding standard pharmacological test results with diversity in substituents to support of the breath of claim 2.

As to R^1, applicants have provided over 100 separate moieties from the presented working examples in traverse of the Examiner's statement that R^1 is not extensively substituted. Applicants provide the following summary table in support of the diversity in the substitution of R^1. As presented in the following table, R^1 moieties are bonded through carbon, nitrogen, sulfur or oxygen to the remainder of the Formula (I) molecular structure.

Diversity to R^1 substitution	
Example Numbers	Moiety
2, 4, 13, 14, 17, 21,33, 44, 50, 80, 84, 90, 93, 94, 97, 100, 101, 104, 106, 107, 118, 125, 160, 172, 226, 227, 228, 247, 274, 275	
3, 12	
6, 22, 23, 24, 103	
7, 48, 55, 58, 65, 83, 89, 185	
8	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
9	
15, 16,	
18, 19	
25, 242	
27, 35, 57, 63, 70, 77, 78, 81, 88, 110, 188, 208, 230, 248	
28, 73, 74, 178	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
29, 266	
30	
32	
34, 64, 192, 235, 265, 269	
37, 236, 237, 238	-NH_2
38	
39	
40	
42, 184	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
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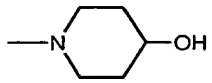
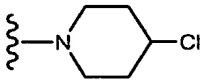
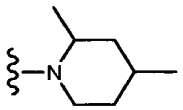
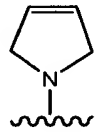
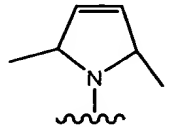
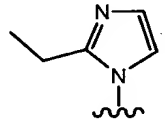
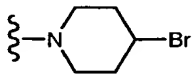
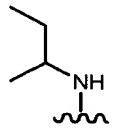
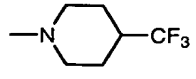
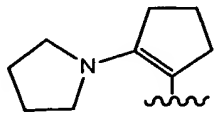
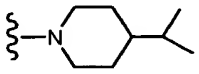
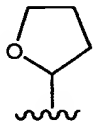
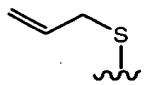
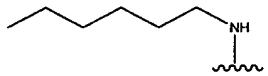
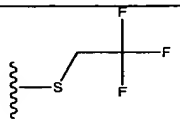
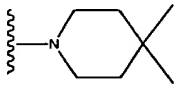
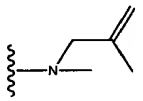
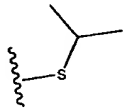
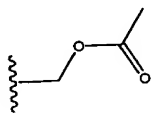
46	
47, 59	
49, 69	
51	
52	
53, 245	
54, 61, 62	
56, 82, 179	
60	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
67, 108	
68	
75, 92	
76	
79	
86	
87	
113	
91, 111	
95	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
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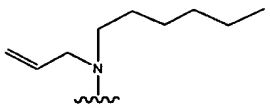
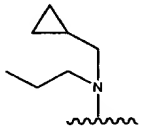
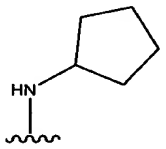
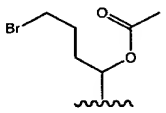
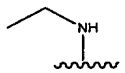
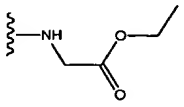
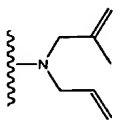
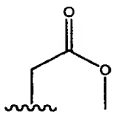
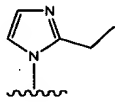
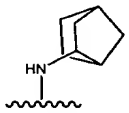
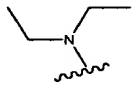
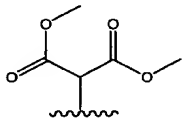
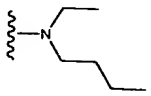
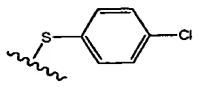
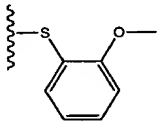
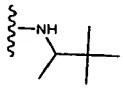
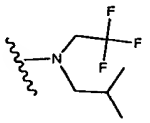
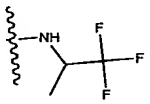
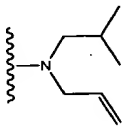
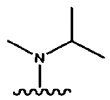
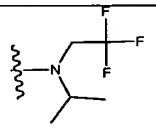
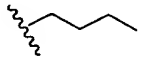
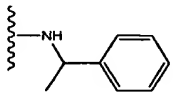
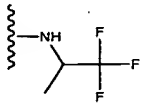
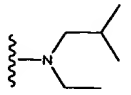
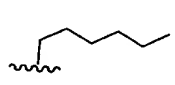
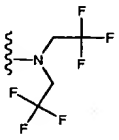
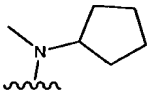
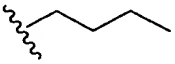
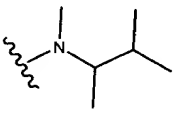
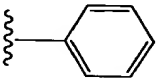
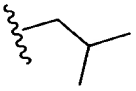
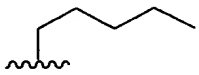
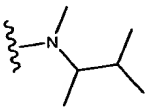
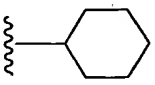
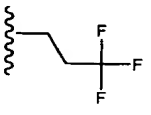
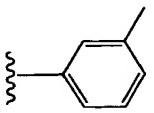
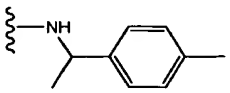
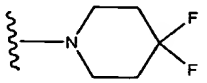
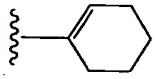
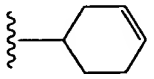
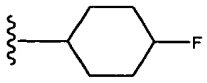
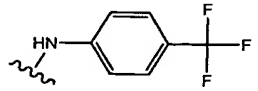
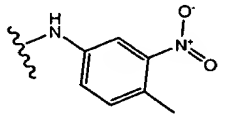
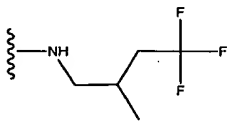
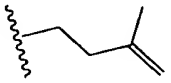
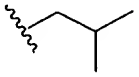
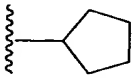
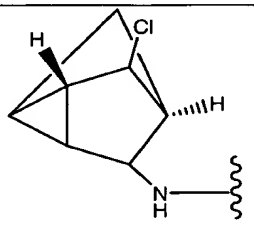
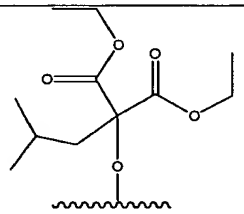
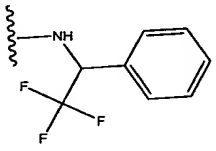
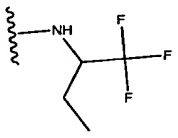
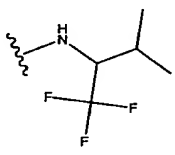
99	
102	
105, 112, 183, 217, 219, 221, 262, 264, 267	
114	
116, 239, 268	
241	
36	

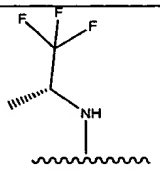
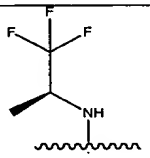
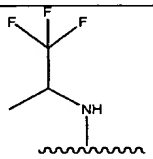
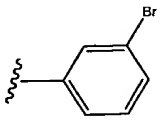
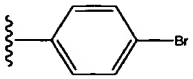
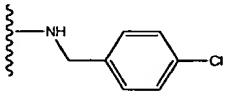
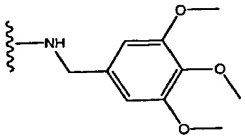
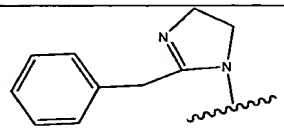
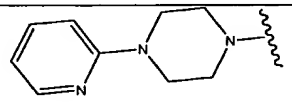
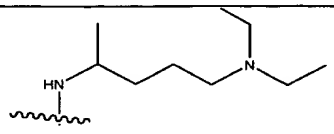
Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
244	
245	
31, 72, 224, 159,	
222, 223, 246,	
249	
117	
119	
120	
121, 122, 123, 124, 126, 127, 128, 135, 187, 205,	

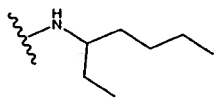
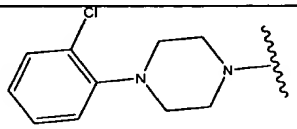
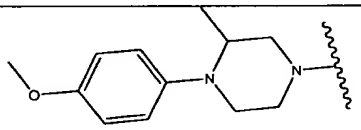
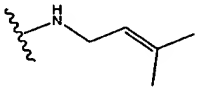
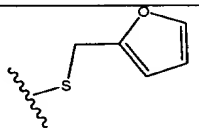
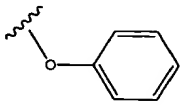
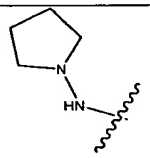
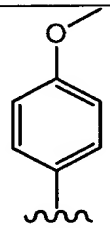
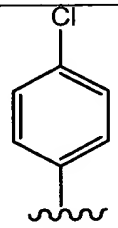
Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
129, 130	
131, 132, 133, 270, 271	
134	
136	
137	
138	
139	
140, 152, 173, 211	
141	
142	

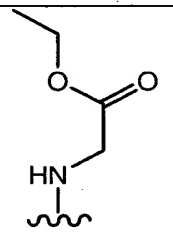
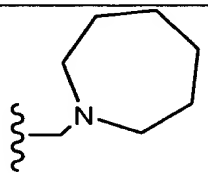
Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
143	
144	
145	
146	
147	
148	
149	
150	
151, 156, 157, 161, 164, 165, 174, 176, 206, 254, 273,	
153	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
154	
155	
158	
168	
167, 181	
182	$-NH_2$
177, 189,	
193	
253	
194	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
195	
196	
197	
272	
250	
162	
163	
166	

Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
169	
170, 175, 199	
152, 171, 173, 180, 190, 191, 270, 200, 201, 202, 203, 204, 207, 209, 210, 271,	
255, 256	
257	
212	
258	
259	
213	
260	

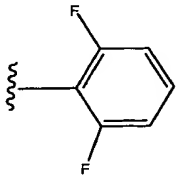
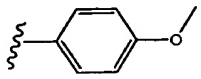
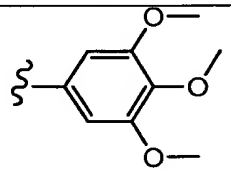
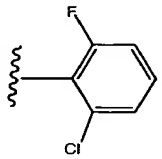
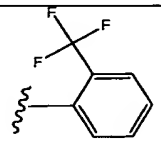
Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
214	
215	
216	
243, 261,	
263	
218, 220	
221	
231, 233	
232	

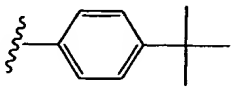
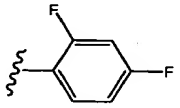
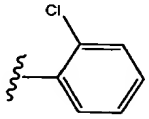
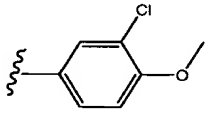
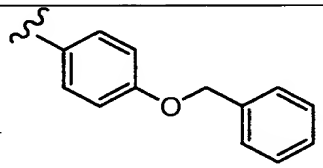
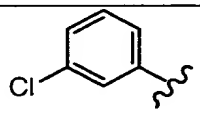
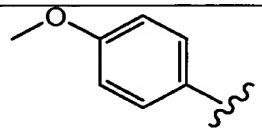
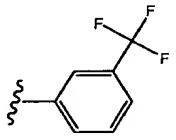
Diversity to R^1 substitution (cont)	
Example Numbers	Moiety
241	
98	

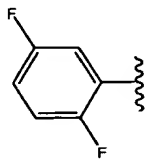
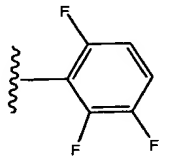
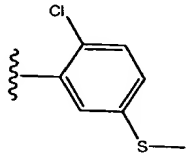
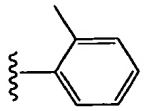
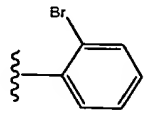
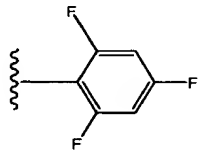
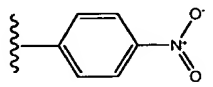
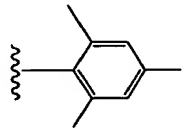
Specifically, applicants have provided working examples with supporting pharmacological testing data in support of the structural diversity for example where R^1 is alkyl (eg. Examples 138, 142, 145, 148, 149, and 196) and substituted alkyl (eg. Examples 45, 95, 96, 109, 114, 153, 244 and 249), alkenyl (eg. Example 95), cycloalkyl (eg. Examples 151, 156, 157, 273, 161, 164, 165, 174, 176, 197, 206 and 254) and substituted cycloalkyl (eg. Examples 189, 177), cycloalkenyl (eg. Examples 176, 168, 181), substituted cycloalkenyl (eg. 108) and further where aryl (phenyl), Example 147, substituted aryl (eg. Examples 154, 231-233, 255-257), heterocyclyl of 5 or 6 ring atoms (eg. Examples 3, 12, 7, 48, 51, 55, 58, 65, 83, 89, 185, 75, 92), heterocyclyl of 5 or 6 ring atoms substituted (eg. Examples 2, 4, 13, 14, 17, 21,33, 44, 50, 80, 84, 90, 93, 94, 97, 100, 101, 104, 106, 107, 118, 125, 160, 172, 226, 227, 228, 247, 274, 275, 6, 22, 23, 24, 103, 15, 16, 18, 19, 30, 39, 46, 47, 59, 49, 69, 52, 53, 245, 54, 61, 62, 60, 68, 87, 158, 245, 259, 213, 215, 216) additionally where Ra and/or Rb are H or alkyl(eg Examples 37, 236, 237, 238, 9, 8, 27, 35, 57, 63, 70, 77, 78, 79, 81, 88, 110, 188, 208, 230, 248, 28, 73, 74, 178, 29, 266, 32, 34, 64, 192, 235, 265, 269, 38, 39, 40, 56, 82, 179, 79, 113, 116, 239, 268, 246, 222, 223, 117, 121, 122, 123, 124, 126, 127, 128, 135, 187, 205, 129, 130, 134, 136, 137, 141, 144, 146, 150, 182, 214) and still further where Ra and/or Rb are H or substituted alkyl (eg. Examples 25, 28, 73, 74, 178, 40, 102, 241, 140, 152, 131, 132, 133, 270, 271,173, 211, 139, 143, 155, 194, 162, 163, 166, 169, 170, 175, 199,152, 171, 173, 180, 190, 191, 270, 200, 201, 202, 203, 204, 207, 209, 210, 271, 212, 258, 260, 241, 242, 29, 266) Additional categories include where Ra and/or Rb are H or alkenyl (eg Examples 36, 261, 243), Ra and/or Rb are H or bicycloalkyl (eg. Examples 31, 72) and Ra is alkyl Rb is alkenyl (eg Examples 99, 113)

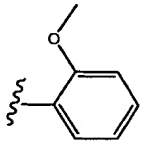
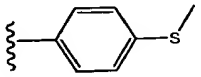
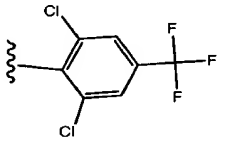
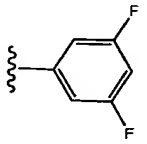
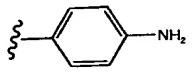
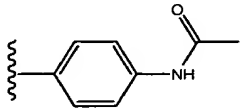
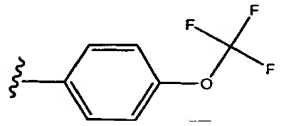
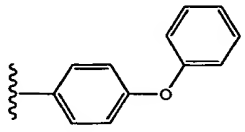
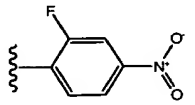
As to R^2 and in traverse of the Examiner's statement that R^2 is not extensively substituted applicants have provided over 50 unique separate working examples. Because of the restriction requirement of September 30, 2003 and applicants' election of R^2 to be substituted phenyl, applicants have provided the following summary table in support of the diversity of the substitutents on the phenyl of R^2. As presented in the table R^2 substituents are not limited to (e.g., difluorophenyl, trifluorophenyl or trifluoromethyl-phenyl) as the Examiner contends. Substituents also include for example alkoxy (e.g. examples 3, 14, 15, 57, 58, 229, 68, 69, 218, 220, 222, 229, 231, 255, 263, 266, 21, 22, 31, 38, 39, 229, 78, 112, 172, 173, 174, 175, 176, 181, 182, 183, 184, 185, 187, 188, 189, 195, 196, 197, 205, 207, and 210), substituted alkoxy (e.g. 65, 100, 190, 191, 200, 211, and 254), alkenyloxy (e.g. 270 and 271), thioalkyl (e.g. examples 80, 81, 82, 83, 230, and 246), chlorothioalkyl (e.g. 228), bromo (e.g. 16, 236, 56 and 128), nitro (e.g. 70), amino (e.g. 93), acetamido (e.g. 94), dimethylamino (e.g. 106), benzyloxy (e.g. 265), phenyl (e.g. 264), unsubstituted (e.g. 232, 233, 261 and 262), phenoxy (e.g. 101, 103, and 248), benzyloxy (e.g. 265), t-butyl (e.g. 13, 23, and 269), methyl (e.g. 55, 126, 130, 143, 219 and 268), chloro(e.g. 62, 74, 140, 221, and 256), trimethyl(e.g. 77), trifluoromethyldichloro (e.g. 84, 88 and 89), fluoro nitro (e.g. 159 and 160), chloro nitro(e.g. 104, 110), bromo choro (e.g. 152), difluoro methoxy (172, 173, 174, 175, 176, 181, 182, 183, 184, 185, 187, 188, 189, 195, 196 and 197), dichloro fluoro(e.g. 178 and 179), difluoro hydroxyl (e.g. 180 and 199), perfluoro (e.g. 144, 146, 117, 272, 122 and 157), dichloro (e.g. 223 and 224), fluoro chloro (e.g. 226), tetrafluoro ethoxy (e.g. 112), tetrafluoro chloro (e.g. 105), difluoro methoxy (e.g. 205 and 210), difluoro hydroxyl (e.g. 199), and fluoro chloro methoxy (e.g. 207).

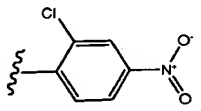
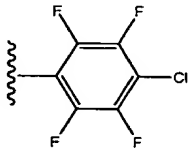
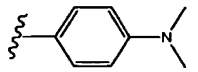
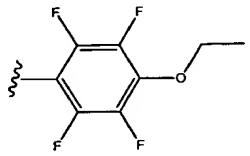
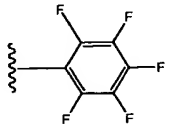
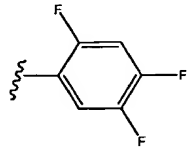
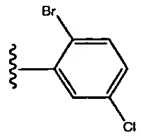
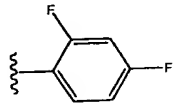
Applicants respectfully traverse the Examiner's statement that R^2 is not extensively substituted. Applicants have provided diversity in the substitution of R^2 as described in the following summary.

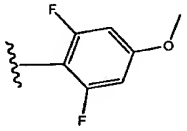
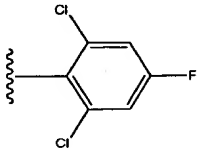
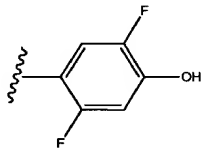
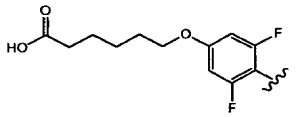
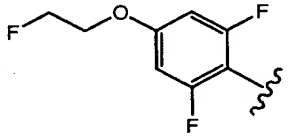
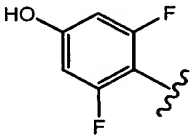
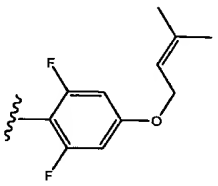
Diversity to R^2 substitution	
Example Numbers	Moiety
2, 25, 42, 46, 47, 49, 51, 61, 73, 145, 242, 245	
3, 14, 15, 57, 58, 68, 69, 218, 220, 222, 229, 231, 255, 263,	
266	
4, 6, 7, 8, 9, 27, 28, 29, 30, 36, 37, 44, 45, 50, 52, 53, 54, 60, 67, 75, 76, 79, 86, 87, 91, 92, 95, 96, 98, 99, 102, 107, 108, 109, 111, 114, 115, 116, 118, 119, 120, 121, 131, 142, 147, 148, 149, 151, 153, 154, 158, 161, 164, 165, 212, 213, 214, 215, 216, 225, 227, 241, 244, 247, 249, 250, 251, 252, 258, 259, 260, 273, 274, 275	
12, 59,	

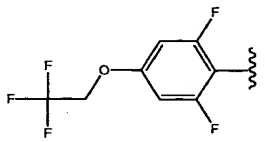
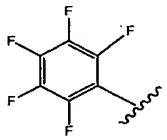
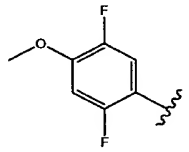
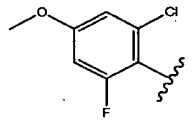
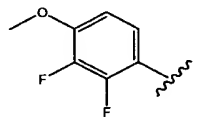
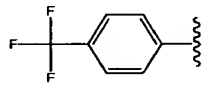
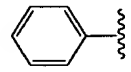
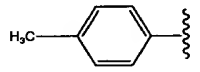
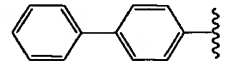
Diversity to R^2 substitution	
Example Numbers	Moiety
13, 23, 269	
16, 236	
171	
62, 74, 140, 221	
21, 22, 31, 38, 39	
265	
256	
229	
24	

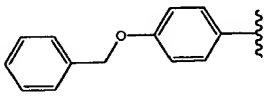
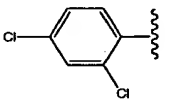
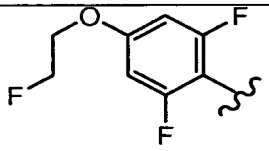
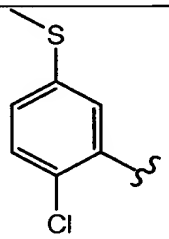
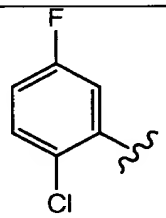
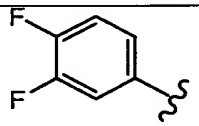
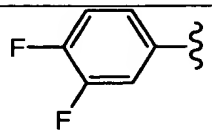
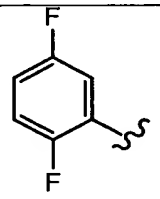
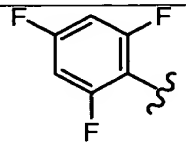
Diversity to R^2 substitution	
Example Numbers	Moiety
32	
33, 34, 35, 40, 48	
228	
55, 126, 130, 143, 268	
56, 128	
63, 64, 65, 72, 113, 123, 125, 129, 133, 134, 135,136, 137, 138, 139, 141, 150, 155, 156, 162, 163, 166, 167, 168, 169, 170,177, 193, 194, 253,	
70	
77	

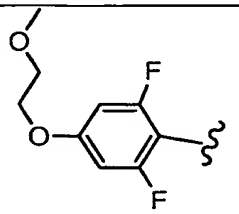
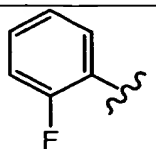
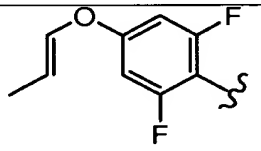
Diversity to R^2 substitution	
Example Numbers	Moiety
78,	
80, 81, 82, 83, 230, 246	
84, 88, 89	
90	
93	
94	
100	
101, 103, 248	
159, 160	

Diversity to R^2 substitution	
Example Numbers	Moiety
104, 110	
105	
106	
112	
117, 122, 272,	
124	
127	
152	
171	

Diversity to R^2 substitution	
Example Numbers	Moiety
172, 173, 174, 175, 176, 181, 182, 183, 184, 185, 187, 188, 189, 195, 196, 197	
178, 179	
180, 199,	
190	
191	
199	
270	

Diversity to R^2 substitution	
Example Numbers	Moiety
200	
144, 146, 157	
205,	
207,	
210	
237, 239, 257	
232, 233, 261, 262	
219	
264	

Diversity to R^2 substitution	
Example Numbers	Moiety
265	
223, 224	
211	
228	
226	
235	
238	
243	
253	

Diversity to R^2 substitution	
Example Numbers	Moiety
254	
267	
271	

As to R^3, applicants have provided diverse moieties. Substituents include for example chlorine, alkoxy, cyano, thioalkyl, azido, amino, dialkylamino, hydrogen, phenoxy, alkyl and piperidinyl.

Applicants have also amended claims 22 and 95 to remove the following non-elected species:

2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-1,3-cyclohexanedione,

2-[5-chloro-6-(2-chloro-6-fluorophenyl)[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]cyclohexanone and

2,5-dichloro-7-(4-methyl-1-piperidinyl)-6-[2-chloro-6-fluorophenyl][1,2,4]triazolo[1,5-a]pyrimidine. Applicants retain the right to pursue these non-elected species in a divisional application.

The Examiner has stated that the art, by way of a search, does not provide teaching as to triazolopyrimidine compounds in oncology and does not provide guidance to the skilled oncologist to select a compound from the large number covered by Formula I.

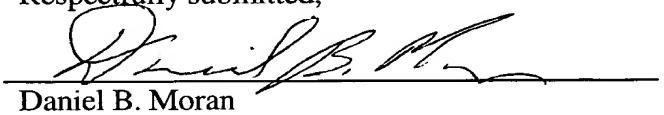
compound of the invention is a substrate of P-gp. The IC_{50} of paclitaxel is more than 1000-fold higher on KB VI than on KB because paclitaxel is a good substrate of P-gp. Representative examples of compounds of this invention were tested on this set of cell lines (see the specification on pages 97-98) and, as shown on page 98 of the specification in Table 4. As described and presented in Table 4 of the specification representative examples tested had essentially the same IC_{50} values for all three cell lines (KB, KB 8.5 and KB VI) which indicates that the compounds are not substrates of P-gp, and they are able to overcome this form of multidrug resistance. As further presented in Table 4, the IC_{50} values for Taxol, Vincristine, Colchicine, Doxorubicin and Nocodazole all increase when proceeding across each individual row from KB to KB 8.5 to KB VI showing them to be substrates of P-gp. Taxol, Vincristine and Doxorubicin are used in cancer therapy, where Colchicine is approved for treatment of gout and Nocodazole is used in research. Representative example 188 is 2X more potent than Nocodazole.

As further described in the specification (pages 98-99), similar experiments were done with the S1 human colon carcinoma cell line, and the S1-M1 cell line derived from it, which expresses another multidrug transporter called MXR. Representative examples of compounds of the invention were tested on the S1-M1 and S1 cell lines and were found to have the same IC_{50} values. The data as presented in Table 5 on pages 98-99 of the specification provide experimental evidence that the compounds are not substrates of the MXR transporter, and therefore overcome multidrug resistance mediated by MXR. In contrast, the IC_{50} value of the clinically-used anti-cancer agent mitoxantrone was over 2000-fold higher on the S1-M1 cell line than on the S1 cell line.

That Nocodazole also is not a substrate for pgp does not diminish the fact that compounds of the invention are expected to be active on cells that develop resistance through this pump. The compounds of the invention are superior to Nocodazole in that they are more potent than Nocodazole which is not a clinically active drug, perhaps because of potency issues. However more importantly, applicants do not believe that it is a requirement of 35 USC 112 to show superiority over Nocodazole or any other drug.
Applicants believe they have complied with 35 USC 112, first paragraph and respectfully ask the Examiner to reconsider and withdraw the rejections to Claims 2-4, 6-8, 10-12, 14-20, 22, 67, 74-77, 79-81, 83-85, 87-93 and 95-98.

Applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein and amendments to the claims, and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,



Daniel B. Moran

Reg. No. 41,204

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (845) 602-845-2224